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| ART UNIT | PAPER NUMBER |
| 1644 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/032,221 | KALLURI, RAGHURAM | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-107* is/are pending in the application.

4a) Of the above claim(s) *43-50,52,53 and 55-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,29-37,51 and 54* is/are rejected.

7)☒ Claim(s) *24-28 and 38-42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/28/06 has been entered.

2. Claims 1-107 are pending.

3. Claims 43-50, 52-53 and 55-107 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-42, 51 and 54 are under examination as they read on an isolated fragmetn of SEQ ID NO: 10 and SEQ ID NO: 37-42 as the species.

5. Applicant's IDS, filed 6/28/06, is acknowledged, however, the International Search Report was crossed out but the references listed thereon had been considered.

6. The amendment filed 11/08/04, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant provides SEQ ID NO: 10 as 244 amino acids rather than 245 amino acid in the claimed provisional applications. However, the corresponding table legend to the sequences does not corresponding the sequence numbering. For example: T8: amino acids $68^{3}$-94 of SEQ ID NO:39. In the table legend indicates for $^{3}$ in T8, lysine has been substituted for the leucine residue at position **69** of the full-length Tumstatin, however this position now is **68**.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

8. Claims 1-6, 10-19, 29-33, 51 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitation of "SEQ ID NO:45" in claims 1, 15 and 29 is indefinite because SEQ ID NO:45 is not a fragment of SEQ ID NO: 33. SEQ ID NO: 45 is a 41 amino acid sequence with 29 undefined amino acids. It is unclear how SEQ ID NO: 45 becomes a fragment of SEQ ID NO: 33. The fragment has broader scope than the polypeptide it derives from.

B. Claims 10-14 are indefinite in the recitation of "SEQ ID NO: 38-42" respectively, because SEQ ID NOs: 38-42 contains amino acid mutations, while the polypeptide of claim 1 is unmutated polypeptide. It is unclear how the unmutated polypeptide of SEQ ID NO: 33 becomes a mutated polypeptides having SEQ ID NO: 38-42.

C. The recitation "the polypeptide is SEQ ID NO:37" in claim 30 is indefinite because claim 30 depends form claim 29, wherein Tumstatin fragment of SEQ ID NO: 33 is claimed which is 88 amino acids in length, claim 30 recites the polypeptide is SEQ ID NO: 37, which is 25 amino acids in length. It is unclear how the 88 amino acid sequence of SEQ ID NO: 33 is now 25 amino acids sequence of SEQ ID NO:37.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:
*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

10. Claims 1-23, 29, 31-37, 51 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases:

A. "An isolated Tumstatin polypeptide of SEQ ID NO: 33 or a fragment thereof wherein the amino acid sequence of said fragment consists/comprises of SEQ ID NO: 45" claimed in claim 1, and claim 15, respectively,

B. "An isolated mutated Tumstatin polypeptide of SEQ ID NO:33, or fragment thereof, wherein said fragment comprises SEQ ID NO: 45" claimed in claims 6 and 20, respectively,

C. "An isolated Tumstatin fragment of SEQ ID NO: 33 or a fragment thereof comprising the amino acid sequence of SEQ ID NO: 45" claimed in claim 29 and

D. "An isolated mutated Tumstatin polypeptide having an amino acid sequence of SEQ ID NO: 33, or fragment thereof, wherein said fragment comprises SEQ ID NO: 45", claimed in claim 34.

represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 6/28/06 points to the specification at figs 3, 35, and page 47 (table 1) and page 62 for support for the newly added limitations as claimed in claims 1, 6, 15, 20, 29

and 34. However, the specification does not provide a clear support for such limitation. The instant claims now recite a limitation, which was not clearly disclosed in the specification and recited in the claims as originally filed.

Applicant submits that fragments of SEQ ID NO: 33 comprising the sequence of SEQ ID NO: 45 finds extensive support in the specification (for example, Tumstatin-45-123 (SEQ ID NO:33, Tum-5, (SEQ ID NO: 26); T3 (SEQ ID NO:29; and T7 (SEQ ID NO: 37)). However, the examiner notes that:

(1) SEQ ID NO:45 is a 41 amino acid in length and none of the disclosed sequences consist of 41 amino acids in length.

(2) SEQ ID NO:45, has $R^1X^1LFX^2NVNX^3VX^4NFR^2$, wherein
$R^1$ is 1-17 any amino acid,
$X^1$ is F or K,
$X^2$ is C, S, or D,
$X^3$ is D or C,
$X^4$, is C, S, or D and
$R^2$ is 1-12 amino acids.
Wherein 12 amino acids are defined ($X^1LFX^2NVNX^3VX^4NF$) and 29 amino acids are unspecified ($R^1$ and $R^2$). A fragment of SEQ ID NO: 33 would have a defined amino acid sequence.

(3) SEQ ID NO: 45 is not a fragment of any sequence but a generic/consensus sequence indicating the specific substitution in each fragment compared to wild-type.

(4) page 62 lines 15-26 discloses Tumstatin (SEQ ID NO: 10), and the fragments T3(SEQ ID NO: 29, 20aa), T7 (SEQ ID NO: 37, 25aa), T8 (SEQ ID NO: 39, 27aa), T8-3 (SEQ ID NO: 40, 27 aa), Tp3 (SEQ ID NO: 41, 19aa) and P2 (SEQ ID NO:42, 27 aa), which all have defined amino acid sequence with or without specific mutations.

(5) Besides, SEQ ID NO: 34, a mutant of Tumstatin-45-132 was created, Tum-5-126-C-A (SEQ ID NO: 33, in which the cysteine at residue number 126, Applicant does not provide support of any mutated Tumstatin polypeptide of SEQ ID NO:33. The claims are directed to a genus of mutated Tumstatin polypeptides of SEQ ID NO:33, which have no support in the specification.

Obviousness is not the standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

9. Claims 1-23, 29, 31-37, 51 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide of SEQ ID NO: 33, an isolated fragment of SEQ ID NO: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and

inhibit protein synthesis in endothelial cells, SEQ ID NO: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ ID NO: 39-42 having the ability to inhibit tumor growth, does not reasonably provide **enablement** for an isolated Tumstatin polypeptide of SEQ ID NO:33, or fragment thereof, wherein the amino acid sequence of said fragment consists of SEQ ID NO: 45, wherein said polypeptide or fragment thereof, has the ability to inhibit tumor growth in claim 1, or has the ability to inhibit angiogenesis in claim 15, or an isolated mutated Tumstatin polypeptide of SEQ ID NO: 33, or a fragment thereof, wherein said fragment comprises SEQ ID NO: 45, wherein said polypeptide or fragment thereof further comprises one to five amino acid substitutions and has the ability to inhibit tumor growth in claim 6, or has the ability to inhibit angiogenesis in claim 20 or having the ability to inhibit protein synthesis in endothelial cells in claim 34 or an isolated Tumstatin fragment of SEQ ID NO: 33 or a fragment thereof comprising the amino acid sequence of SEQ ID NO: 45, and having the ability to inhibit protein synthesis in endothelial cells in claim 29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification on page 50 discloses that Tumstatin-44-131 (SEQ ID NO33) binds to the $\alpha v\beta 3$ and the $\beta 1$ integrins on the surface of endothelial cells as determined by the competition proliferation assay. The instant claims recite that the fragment of SEQ ID NO: 33 consist of SEQ ID NO: 45, a 41 amino acid sequence with 29 unspecified amino acids, or a mutated SEQ ID NO:33 or a fragment thereof comprises SEQ ID NO: 45 and further comprises one to five amino acid substitutions. However, it is recognized in the art that ligands must posses significant structural and chemical complementarity to their target receptors (Kuntz, Science, 1992, Vol. 257:1078-1082, especially page 10709, 2nd col., lines 1-4 and 9-12 under heading "Structure-Based Design (of record)) and that ligands generally bind to native states of proteins with little or no interaction with unfolded states (Miller et al, Protein Science, 1997, 6:2166-2179, especially page 2166, 2nd col., lines 18-20) and further that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Finally, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page 1080, 3rd col.). The claims encompass alterations in protein folding because claims do permit deviation from the amino acid sequences of the consensus regions for a non-native protein. It would be reasonable to conclude that alterations in protein folding would lead to a large alteration in binding affinity.

There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Wang et al. (JBC 276:4913-49220), who show that a single amino acid determines lysophospholipid specificity of the S1P1 (EDG1) and LPA1

(EDG2) phospholipids growth factor receptors (e.g., abstract). Wang et al shows that a single amino acid $Glu^{121}$ in S1P1/EDG1, which corresponds to $Gln^{125}$ in LPA1/EDG2, influences the specificity for S1P or LAP (see page 49213 last ¶). Mutating the Arg-Glu-Gly motif to that is conserved among LPA receptors Arg-Gln-Gly, lead to ligand selectivity switch in concert with the mutations. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the polypeptide to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Further, one cannot extrapolate the teachings of the specification to the scope of the claims because the modulating agents are peptides that have mutually exclusive function. Patent No. 6,962,974 teaches that a fragment comprising LQRFTTMPF**LFCNVNDVCNF** (patented SEQ ID NO: 26) is characterize by it inability to inhibit proliferation of tumor cells (see patented claim 7). Instant claims 1-14, recite that SEQ ID NO:33 and 45 comprising the core structure XF**LFCNVNDVCNF**X has the ability to inhibit tumor growth. Those activities are mutually exclusive in that they reach opposing endpoints. It has not been shown that these polypeptides/fragments are capable of functioning as that which is being claimed.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 6/28/06, have been fully considered, but have not been found convincing.

Regarding claims 6, 20 and 34 recitation of "one to five amino acid substitutions", Applicant draws the Examiner's attention to *Ex parte Mark* (12 USPQ2d 1904 (BD. Pat. App. & Int. 1989).

However, the fact pattern in *Ex parte Mark* is not the same the fact pattern in the instant case. In the instant case, SEQ ID NO: 45, $R^1X^1LFX^2NVNX^3VX^4NFR^2$ is a 41 amino acid in length, wherein 12 amino acids are defined ($X^1LFX^2NVNX^3VX^4NF$) and 29 amino acids are unspecified ($R^1$ and $R^2$). Among the 12 defined amino acids only 8 amino acid are being fixed the other four ($X^{1-4}$) are being given specific amino acids alternatives. Given that the 12 amino acid are important for the activity of the polypeptide, mutations in the conserved patterns without

much change in the overall sequence would lead to a change in the essential active site structure and therefore to a change in function. Making changes up to five mutagenesis in polypeptide/fragmetn sequences do not provide the resultant mutant polypeptide/fragment will retain the same inhibitory activity as the unmutated polypeptide. One of ordinary skill in the art cannot envision all of the amino acid changes encompassed by the breadth of the claims and still inhibiting tumor growth, angiogenesis and protein synthesis activity. With only 7 (given that the 4 ($X^{1-4}$) alternative amino acid can be mutated) amino acids out of 41 amino acid (17%) of SEQ ID NO: 45 are defined after up to five amino acid substitutions, the claimed polypeptide/fragment is not enabled for the claimed activity. None of Applicant's examples show that such a polypeptide/fragment has activity.

10. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of and isolated polypeptide of SEQ ID NO: 33, an isolated fragment of SEQ ID NO: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and inhibit protein synthesis in endothelial cells, SEQ ID NO: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ ID NO: 39-42 having the ability to inhibit tumor growth.

Applicant is not in possession of an isolated mutated Tumstatin polypeptide of SEQ ID NO: 33, or a fragment thereof, wherein said fragment comprises SEQ ID NO:45, wherein said polypeptide or fragment thereof, further comprises one to five amino acid substitutions, and wherein the "mutated polypeptide has the ability to inhibit angiogenic activity" in claim 20.

It is noted further that claim 20 recites that only the "mutated polypeptide has the ability to inhibit angiogenic activity", however, the mutated fragment is not said to have any activity.

Applicant has disclosed only amino acid of SEQ ID NO: 33 and 37-42; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

12. Claims 6, 20 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45).

Kalluri *et al* teach mutated fragment/polypeptide, α3/n-26/c-KK having a deletion of N-terminal triple helix 26 aa and substitution of last two lysines to alanines (see the entire document and page 9064 under Figure 1 in particular). While the prior art teachings may be silent as to the ability to "inhibit tumor growth", "inhibit angiogenic activity","inhibit protein synthesis in endothelial cells" per se; the product in Kalluri *et al* reference is the same as the claimed product. Therefore the functional property of the claimed polypeptide/fragment is considered inherent properties.

The term "mutated" opens up the polypeptide of SEQ ID NO: 33 to insertion of unspecified amount of amino acids insertion on either or both sides of C-termini or N-termini of SEQ ID NO: 33. Further, α3/n-26/c-KK, which comprises SEQ ID NO: 45, having a deletion of N-terminal triple helix 26 aa (polypeptide/fragment) and substitution of last two lysines to alanines.

When a claim recites using an old composition or structure (e.g. polypeptide/fragment of SEQ ID NO: 33) and the use is directed to a result or property of that composition or structure (inhibiting tumor growth, angiogenesis and protein synthesis in endothelial cells), then the claim is anticipated. See MPEP 2112.02. Also, see Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc. 58 USPQ2d 1508 (CA FC 2001); Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

The reference teachings anticipate the claimed invention.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 6-7, 20-21and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) in view of U.S. Patent 5,858,670.

The teachings of Kalluri et al references have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is reduced.

The `670 patent teaches that a reduced peptide bond may be introduced as a dipeptide subunit. Such a molecule would be resistant to peptide bond hydrolysis, e.g., protease activity. (Col., 10 lines 50-61 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide taught by Kalluri et al as reduced polypeptide as taught by `670 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such reduced fragments would be resistant to peptide bond hydrolysis as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 6, 8, 20, 22, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45 in view of U.S. Patent 5,326,875.

The teachings of Kalluri et al reference have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is alkylated.

The `875 patent teaches that alkylated peptides can be purified by crystallization or by silica gel chromatography. Further the `875 patent teaches that protected alkylated peptides are readily soluble in acidic aqueous medium (Col., 3 lines 43-68 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide taught by Kalluri et al as alkylated polypeptide as taught by `875 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such alkylated polypeptide are readily soluble in acidic aqueous medium as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 6, 9, 20, 23, 34 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalluri *et al* (J Biol. Chem. 271:9062-9068, 1996) (IDS Ref. No. 45) in view of U.S. Patent 5807,821.

The teachings of Kalluri et al reference have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is oxidized.

The `821 patent teaches that a variety of protecting groups can be incorporated into the synthesis of linear peptide to facilitate isolation, purification, and/or yield of the desired peptide. Protection of cysteine residues found in the peptide can be accomplished using, for example, a triphenylmethyl, acetamidomethyl and/or 4-methoxybenzyl group in any combination. Such a strategy may offer advantages for subsequent oxidation studies to yield folded peptide. (Col., 8 lines 45-60 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide taught by Kalluri et al as oxidized polypeptide as taught by `821 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such oxidation of the polypeptide offer advantages for subsequent oxidation studies to yield folded peptide as taught by the `821 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 6/28/06 have been fully considered, but have not been found convincing.

Applicant argues that the claims now recite SEQ ID NO:33. Applicant concluded that the truncated Tumstatin of Kalluri et al is now distinguished from the prior art.

Contrary to applicant conclusion the prior art of Kalluri's truncated fragments still reads on the claimed mutated polypeptide/fragment of α3 chain of SEQ ID NO: 33. Because the term "mutated" opens up the claims to amino acid insertion on either or both N- or C terminals.

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1, 6, 15, 16, 20, 29,30, 34, 51 and 54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,962,974. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the application and patent are drawn to the same fragments comprising the core domain of LQRFTTMP*F*LF*C*NVN*D*V*C*NF (patented SEQ ID NO: 26), wherein the fragment characteristics of (a) the ability to bind αvβ3 integrin, (b) inhibit proliferation of endothelial cells reads on the claimed fragment consists of SEQ ID NO:45 "$R^1X^1$LF$X^2$NVN$X^3$V$X^4$NF$R^2$" claimed in claims 1, 15 and 29, since one of the fragment non-Goodpastrure α3(IV) NC1 domain would be SEQ ID NO:33 or 45. Further, claims 6, 20 and 34 is included because $R^1$ of claimed SEQ ID NO: 45 is any amino acids, the LQRFTTMP on the N-terminal of patented SEQ ID NO: 26 considered to comprise 1-5 substitutions and up to 7 mutations. The claimed functional property are considered inherent property of fragments comprising the patented SEQ ID NO:26. Further, the `974 specification on col., 3, lines 1-4 teaches that another peptide fragment of full-length Tumstatin is designated as Tumstatin-45-132 (claimed SEQ ID NO: 33), comprising claimed SEQ ID NO: 45. Both claimed SEQ ID NOs: 33 and 45 are a non-Goodpastrure fragment comprising non-Goodpastrure α3(IV) NC1 domain of patented SEQ ID NO: 26.

19. Claims 6-7, 20-21and 34-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,962,974 in view of U.S. Patent 5,858,670.

The teachings of `974 patent have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is reduced.

The `670 patent teaches that a reduced peptide bond may be introduced as a dipeptide subunit. Such a molecule would be resistant to peptide bond hydrolysis, e.g., protease activity. (Col., 10 lines 50-61 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide/fragment taught by the `974 patent as reduced polypeptide as taught by `670 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such reduced fragments would be resistant to peptide bond hydrolysis as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 6, 8, 20, 22, 34 and 36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,962,974 in view of U.S. Patent 5,326,875.

The teachings of the `974 patent have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is alkylated.

The `875 patent teaches that alkylated peptides can be purified by crystallization or by silica gel chromatography. Further the `875 patent teaches that protected alkylated peptides are readily soluble in acidic aqueous medium (Col., 3 lines 43-68 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide/fragment taught by the `974 patent as alkylated polypeptide as taught by `875 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such alkylated polypeptide are readily soluble in acidic aqueous medium as taught by the `670 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 6, 9, 20, 23, 34 and 37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4-8 of U.S. Patent No. 6,962,974in view of U.S. Patent 5807,821.

The teachings of the `974 patent have been discussed, supra

The claimed invention differs from the reference teachings only by the recitation that the polypeptide is oxidized.

The `821 patent teaches that a variety of protecting groups can be incorporated into the synthesis of linear peptide to facilitate isolation, purification, and/or yield of the desired peptide. Protection of cysteine residues found in the peptide can be accomplished using, for example, a triphenylmethyl, acetamidomethyl and/or 4-methoxybenzyl group in any combination. Such a strategy may offer advantages for subsequent oxidation studies to yield folded peptide. (Col., 8 lines 45-60 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the polypeptide/fragment taught by the `974 patent as oxidized polypeptide as taught by `821 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such oxidation of the polypeptide offer advantages for subsequent oxidation studies to yield folded peptide as taught by the `821 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Claims 24-28 and 38-42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 17, 2006

Maher Haddad

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